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Impact of left ventricular hypertrophy on survival in end-stage renal disease

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Impact of left ventricular hypertrophy on survival in end-stage renal disease. We examined the prognostic significance of left ventricular hypertrophy determined by echocardiography in a cohort beginning renal replacement therapy. No patient had hemodynamically significant valvular disease or echocardiographic signs of obstructive cardiomyopathy. Using the Cox proportional hazards model, left ventricular hypertrophy was significantly associated with survival. The relative risk, based on comparison of upper and lower quintiles of left ventricular mass index, was 3.7 (95% confidence intervals, 1.6 to 8.3) for all-cause mortality and 3.7 (95% confidence intervals, 1.2 to 11.1) for cardiac mortality. The independent risk, adjusted for age, known coronary artery disease, diabetes, level of systolic blood pressure, and treatment (dialysis or transplantation), was 2.9 (95% confidence intervals, 1.3 to 6.9) for all-cause mortality and 2.7 (95% confidence intervals, 0.9 to 8.2) for cardiac mortality. Therefore, left ventricular hypertrophy appears to be an important, independent, determinant of survival in patients receiving therapy for end-stage renal failure.

Left ventricular hypertrophy is an important marker of risk for death and other adverse events in patients with hypertension [1, 2] as well as in otherwise normal people [3–5]. Although the mechanisms have not been established definitively, asymptomatic ventricular arrhythmias are prevalent [6, 7], as are abnormalities of vasodilator reserve [8, 9] and abnormalities of the coronary microcirculation [10].

Cardiovascular events remain the major cause of mortality and morbidity in patients with end-stage renal disease [11]. We have reported a high prevalence of left ventricular hypertrophy determined by echocardiography in patients treated by chronic ambulatory peritoneal dialysis; in that study, left ventricular hypertrophy seemed to be strongly associated with mortality during a short follow-up period [12]. The present study was thus designed to evaluate the independent prognostic significance of left ventricular hypertrophy in a larger population with end-stage renal disease treated by all modalities (hemodialysis, intermittent and continuous peritoneal dialysis, and transplantation).

Methods

The Royal Victoria Hospital is a tertiary referral institution affiliated with McGill University which offers all forms of renal replacement therapy with the exception of home hemodialysis. Since 1983 a prospective protocol has existed to determine the characteristics of patients receiving treatment for end-stage renal disease. All patients beginning therapy between January 1983 and August 1987 were screened for inclusion in the study. Patients were excluded if they had hemodynamically significant valvular disease, if they had begun dialysis at another institution, if they were restarting after failed transplantation, if they had known pre-existing malignant disease, or if they had acute renal failure and either died or recovered renal function. Patients with acute renal failure who did not recover renal function but survived and required maintenance replacement therapy were included. Patients beginning treatment here who transferred to other institutions were followed as to vital status.

Aside from left ventricular hypertrophy, other potentially important prognostic variables studied were age, sex, type and duration of underlying kidney disease, duration of hypertension or diabetes mellitus, level of systolic and diastolic blood pressure, definite and suspected coronary artery disease, smoking history, and serum calcium, phosphate, and parathyroid hormone levels. Myocardial infarction was considered 'Definite' if the electrocardiogram revealed abnormal Q-waves or if there was regional wall motion abnormality on the two-dimensional echocardiogram with appropriate electrocardiographic changes. Electrocardiographic left ventricular hypertrophy was based on Romhilt-Estes Criteria [13].

Echocardiography

All studies were performed using an ATL-600 apparatus (Advanced Technology Laboratories, Bothell, Washington, USA). Two-dimensional imaging was used to guide the M-mode beam. Evaluation of valves included pulsed and continuous wave Doppler. All studies were reported by one of two observers according to American Society for Echocardiography criteria [14]. Left Ventricular Mass Index (LVMI) was determined according to the method of Devereux and Reichek [15].

Outcome

Vital status was established by a physician for all subjects. Cardiac death was defined according to criteria based on those used in the Lipid Research Clinics trial [16] as sudden (unexpected) death, death associated with a definite myocardial ischemic event, or death in heart failure (refractory to ultrafiltration).

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Table 1. Cohort selection

390 Screened
- 271 Excluded
  - 111 Acute renal failure
  - 100 Began pre-1983
  - 10 Prior transplantation
  - 28 Began elsewhere
  - 17 Pre-existing malignancy
  - 4 Valve disease: 1 Mixed mitral valve disease; 1 Mitral valve replacement; 2 Aortic stenosis
  - 1 Chart not available
- 119 Eligible
  - 91 Early echocardiography
  - 22 Late echocardiography only
  - 6 No echocardiography

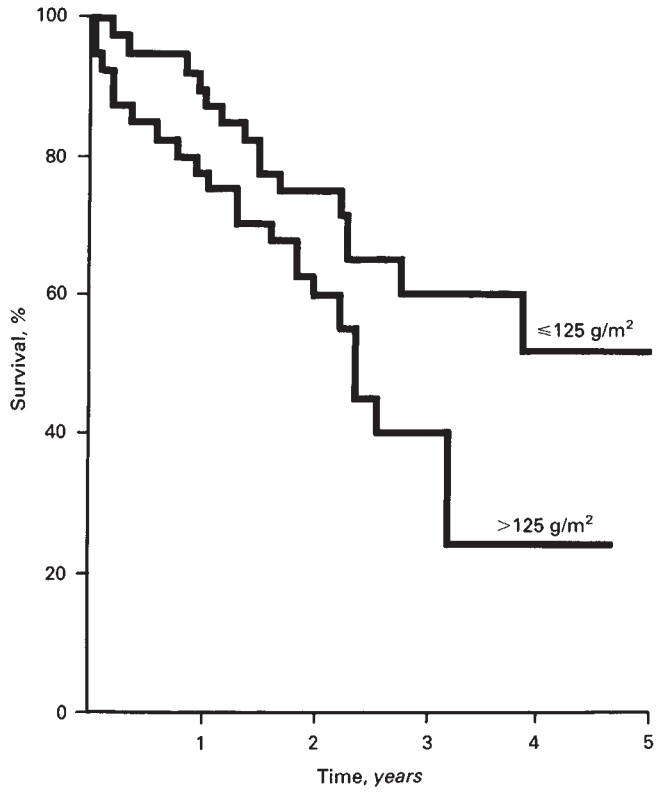

Fig. 1. *Cumulative survival according to echocardiographic left ventricular hypertrophy defined as LVMI > 125 g/m².* This cutpoint corresponds to the 95th centile of 2 normal populations reported by Casale et al [1].

Statistics

Analysis was performed using SAS (SAS Institute Inc., Cary, North Carolina, USA, 1985) and BMDP (University of California, 1983) statistical software. The Cox proportional hazards model was used to estimate the survival function, with transplantation as a time-dependent covariate [17]. Confidence intervals for rate ratios were test-based [18]. Survival curves were constructed according the method of Kaplan and Meier [19].

Table 2. Clinical characteristics (all values are expressed as mean ± SD)

No. patients	91
Age: mean	55 ± 15
range	20–87
Sex M/F	55/36
(% Male)	60
Kidney disease[a]	
Glomerulonephritis	25 (27%)
Diabetes	21 (23%)
Nephrosclerosis	15 (16%)
Pyelonephritis	13 (14%)
Other	17 (18%)
Definite myocardial infarction	10 (11%)
Angina	27 (30%)
Hypertension	67 (73%)
Systolic blood pressure *mm Hg*	152 ± 24
Diastolic blood pressure *mm Hg*	86 ± 11
Urea *mmol/liter*	35 ± 14
Hemoglobin *g/liter*	90 ± 25
Transplanted during follow-up	18 (20%)
Echocardiography	
LVMI *g/m²*	121 ± 32
Range	65–198
LV End-systole *mm*	34 ± 7
Range	20–60
LV End-diastole *mm*	51 ± 7
Range	35–72
LV Posterior wall *mm*	11.4 ± 1
Range	9–15

[a] Nephrosclerosis includes hypertension but not diabetes; Pyelonephritis includes analgesic nephropathy.

Abbreviations are: LVMI, left ventricular mass index; LV, left ventricle.

Results

Of 390 patients receiving renal replacement therapy during the study period, 119 met the entry criteria. The reasons for exclusion of the remaining patients are shown in Table 1. Of those eligible, 91 patients (77%) underwent the intended echocardiographic study either prior to or within the first two months of beginning replacement therapy (median: 51 days pre-starting). Twenty-two patients (19%) were studied for the first time later in the course of dialysis while six patients (4%) died within two months of beginning therapy without having an echocardiographic study.

The 91 patients who had an early echocardiographic examination were studied in the survival analysis (Fig. 1). Their clinical characteristics are given in Table 2. All patients with prior definite myocardial infarction or coronary bypass grafting had subsequent angina. No patient had asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, or midsystolic aortic valve closure at echocardiography. Median follow-up was 576 days (range: 2 to 1839) from the commencement of replacement therapy.

Determinants of mortality: Crude associations

Based on a comparison of uppermost (>166 g/m²) and lowermost (<83 g/m²) quintiles of left ventricular mass index, the risk ratio (relative risk) for left ventricular hypertrophy was 3.7 for both all-cause mortality and cardiac mortality (Tables 3 and 4). The risk ratio for end-systolic dimension for all-cause

Table 3. Crude associations: All-cause mortality

Variable	Coefficient	P^a	Relative risk[b]	95% Confidence interval Lower	Upper
Age *years*	0.0785	<0.0002	26.6	7.9	89.6
Male sex	0.1049	0.77	1.1	0.8	1.4
LVMI g/m^2	0.0156	0.0026	3.7	1.6	8.3
ESD *mm*	0.0664	0.14	2.6	0.9	7.4
Syst BP *mm Hg*	0.0094	0.36	1.8	0.8	4.3
Hypertension	0.4569	0.68	1.6	0.6	4.3
Angina	1.5820	<0.0002	4.9	2.4	9.8
Definite MI	1.1616	0.0320	3.2	1.6	6.5
Diabetes	0.8400	0.0234	2.3	1.2	4.5
Transplant	−2.53	0.0036	0.08	0.01	0.6

Abbreviations are: LVMI, left ventricular mass index; ESD, end-systolic dimension; Syst BP, systolic blood pressure; MI, myocardial infarction.

[a] *P* values are two sided

[b] For continuous variables, relative risk estimates are based on comparison of top and bottom quintiles.

Table 4. Crude associations: Cardiac mortality

Variable	Coefficient	P^a	Relative risk[b]	95% Confidence interval Lower	Upper
Age *years*	0.0653	0.0004	15.3	3.3	70.5
Male sex	0.2730	0.58	1.3	0.6	3.3
LVMI g/m^2	0.0157	0.0354	3.7	1.2	11.1
ESD *mm*	0.0960	0.0808	3.8	1.1	13.9
Syst BP *mm Hg*	0.0075	0.870	1.6	0.5	5.2
Hypertension	1.6272	0.158	5.1	0.7	38.4
Diabetes	1.2753	0.0084	3.6	1.4	9.2
Angina	2.2167	<0.0002	9.2	3.4	24.7
Definite MI	1.7170	0.0032	5.6	1.9	16.3
Transplant[c]					

Abbreviations are: LVMI, left ventricular mass index; ESD, end-systolic dimension; Syst BP, systolic blood pressure; MI, myocardial infarction.

[a] *P* values are two-sided

[b] For continuous variables, relative risk estimates are based on comparison of top and bottom quintiles.

[c] No transplanted patient suffered a cardiac death. The coefficient is thus inestimable.

mortality was 2.6 (one-sided $P = 0.07$), and for cardiac mortality, 3.8 (one-sided $P = 0.04$). Age (uppermost quintile: >76 years; lowermost quintile: <35 years) was a very powerful predictor, with an estimated relative risk of 26 for all-cause and 15 for cardiac mortality. The relative risk associated with angina was 4.9 for all-cause and 9.2 for cardiac mortality, and with definite myocardial infarction 3.2 (all-cause) and 5.6 (cardiac). Diabetes was more strongly associated with cardiac (relative risk 3.6) than with all-cause mortality (relative risk 2.3). Neither the diagnosis of hypertension nor the actual level of systolic blood pressure were associated with all-cause mortality, although there was a trend to greater cardiac mortality in hypertensives (relative risk 5.1, one-sided $P = 0.07$). Neither cause (other than diabetes) nor duration of known kidney disease were significantly associated with mortality, nor were blood urea, hemoglobin, calcium, phosphate, alkaline phosphatase, parathyroid hormone levels, or smoking status. Only

Table 5. Adjusted associations: All-cause mortality

Variable	Coefficient	P^a	Relative risk[b]	95% Confidence interval Lower	Upper
Age	0.0594	0.0002	12.0	3.1	46.4
LVMI	0.0126	0.0132	2.9	1.3	6.7
Hypertension	0.2512	0.6170	1.3	0.5	3.7
Angina	0.6958	0.0768	2.0	0.9	4.3
Diabetes	0.5672	0.1164	1.8	0.9	3.8
Transplant	−1.3317	0.2150	0.3	0.03	2.2

Abbreviation is: LVMI, left ventricular mass index.

[a] *P* values are two-sided

[b] For continuous variables, relative risk estimates are based on comparison of top and bottom quintiles.

Table 6. Adjusted associations: Cardiac mortality

Variable	Coefficient	P^a	Relative risk[b]	95% Confidence interval Lower	Upper
Age	0.0417	0.0384	5.7	0.8	29.9
LVMI	0.0119	0.0784	2.7	0.9	8.2
Hypertension	1.3243	0.2076	3.8	0.5	30.2
Angina	1.6223	0.0034	5.1	1.7	15.2
Diabetes	0.9827	0.0488	2.7	1.0	7.3

Abbreviation is: LVMI, left ventricular mass index.

[a] *P* values are two sided

[b] For continuous variables, relative risk estimates are based on comparison of top and bottom quintiles.

one of 18 patients transplanted during the follow-up period died, the cause being noncardiac. The relative risk with transplantation was thus inestimable for cardiac mortality, while for all-cause mortality it was 0.08 (12 to 1 against).

Multivariate analysis

The relationship between left ventricular mass index and all-cause mortality persisted after adjustment for age, hypertension, angina, diabetes and transplantation (adjusted relative risk: 2.9, Tables 5 and 6). Transplantation was not included in the analysis of cardiac mortality, where the adjusted relative risk for left ventricular mass index was 2.7 (one-sided $P = 0.04$).

Components of left ventricular mass index

The prognostic effects of wall thickness and end-diastolic cavity dimension were examined in a limited model adjusting for the other. For both all-cause mortality and cardiac mortality, the risk associated with posterior wall thickness was independent of cavity dimension (Table 7).

Thickness versus end-systolic dilatation

A further model examined the adjusted effects of posterior wall thickness and end-systolic cavity dimension. Both wall thickness (risk ratio for all-cause mortality 2.6, $P = 0.0037$) and cavity dilatation at end-systole (risk ratio for all-cause mortality 3.2, $P = 0.012$) exerted important prognostic effects independent of each other.

Table 7. Components of LVMI

Variable	Coefficient	P^a	Relative risk[b]	95% Confidence interval Lower	Upper
All-cause mortality					
PW thickness	0.2581	0.0272	2.2	1.1	4.4
LV diastole	0.0328	0.0749	1.8	0.8	4.0
Cardiac mortality					
PW thickness	0.2770	0.0392	2.3	0.9	5.8
LV diastole	0.0301	0.1635	1.7	0.6	4.9

Abbreviations are: PW, posterior wall; LV left ventricle.
[a] P values are two-sided
[b] Relative risk estimates are based on comparison of top and bottom quintiles.

Patients who did not have early echocardiography

The 22 patients who were studied for the first time later in the course of replacement therapy were of similar clinical characteristics at entry to those who were included in the main survival analysis. These 22 patients were examined separately in an analysis of survival from the time of echocardiography. In this small population the relative risk of mortality associated with left ventricular mass index (uppermost vs. lowermost quintile) was 2.5 (one-sided $P = 0.11$). Four of the six patients who died before echocardiography could be performed had electrocardiographic left ventricular hypertrophy.

Discussion

We have found left ventricular hypertrophy, quantitated by echocardiography and expressed as left ventricular mass index, to be an important determinant of outcome in patients with end-stage renal disease. The effect was strong and persisted after adjustment for associated known prognostic factors. The prognostic importance of left ventricular hypertrophy evident in the present study is consistent with findings in patients with hypertension [1, 2], in apparently normal persons [3–5], and in trained athletes [20]. Ventricular arrhythmias, probably reflecting subendocardial ischemia due to abnormal vasodilator reserve [8, 9] or structural changes in the coronary microcirculation [10] appear to be the most likely mechanism of increased risk for death, both unexpected and associated with intercurrent acute illness.

The factors for which we adjusted included age, diabetes mellitus, blood pressure, and coronary disease. Since coronary angiography was not part of our routine evaluation, we will necessarily have misclassified some patients. We chose to use angina rather than definite myocardial infarction as our marker for coronary disease in order to maximize sensitivity. Angina may occur in left ventricular hypertrophy without coronary artery disease, but the effect of this would be to reduce rather than enhance the apparent hypertrophy/survival relationship.

Given the reported high prevalence of coronary disease in patients with end-stage renal disease [21] and the possibly accelerated atherosclerosis in patients maintained on hemodialysis [22], we believe coronary artery disease to be the most important factor in determining survival in these patients. However, examining the effect of left ventricular hypertrophy while adjusting for suspected coronary artery disease, we found important independent effects. Indeed, it is likely that hypertrophy magnifies the impact of associated coronary artery disease in these patients. The importance of 'parallel' or 'concentric' hypertrophy manifest as wall thickening [23] versus that secondary to cavity dilatation (measured at both end-diastole and end-systole) was evident when the reduced models were examined. Posterior wall thickness and end-systolic dimension, adjusted for the other, predicted outcome equally well, with similar relative risks. Of interest, end-systolic volume, which reflects ventricular systolic performance, has recently been suggested as the best predictor of outcome following myocardial infarction [24].

A strength of our study is that we identified all patients receiving dialysis during the study period, and follow-up was complete for all patients meeting the entry criteria. We were less successful in achieving echocardiographic studies at the intended time since only 77% of our patients were studied at the initiation of dialysis. The findings in the remaining patients, however, supported the importance of left ventricular hypertrophy in determining outcome.

While echocardiography is unquestionably the best clinical method available to estimate left ventricular mass, its limits must not be overlooked. The method requires accurate measurement of the thickness of the left ventricular wall and the diameter of the left ventricular cavity. From this left ventricular volume is calculated and the estimate of left ventricular mass depends on geometric assumptions involved in these calculations and the assumption of uniform wall thickness. Thus left ventricular mass is a function of left ventricular thickness and left ventricular volume, and measurement of wall thickness alone would incompletely represent left ventricular mass. It must also be appreciated that left ventricular mass is a composite of all the tissue elements within the heart. Thus Mall et al [25] have demonstrated that the increase in left ventricular mass documented in hypertensive uremic animals correlated, in fact, better with increased interstitial tissue than with changes in myocyte size.

The results of this study establish the need to understand more precisely the determinants of left ventricular hypertrophy in end-stage renal disease. Hypertension, the presence of an arteriovenous fistula and anemia must all be considered as potentially important contributors. Anemia may be of particular importance since this complication of end-stage renal disease can now be treated with recombinant erythropoietin. However, whether left ventricular hypertrophy will regress with such therapy and whether regression of left ventricular hypertrophy would improve outcome in end-stage renal disease remains to be established.

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